MEDICINE CABINET

Drug treatment of depression

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Depression is an important mental health problem. Because it is often unrecognized or not properly treated, it causes distress, social impairment, and an increased risk of death for the individual, as well as generating large costs for society. Several efficient treatments and strategies exist, however, among which antidepressant drugs are the main option.

Methods

This article is based on a review of recent research on the use of antidepressant drugs in treating depression. Research papers and recent comprehensive reviews are cited.[1] In areas of uncertainty, we make suggestions based on personal experience.

General considerations

Most patients with major depression[2] (see box) are best treated with a combination of antidepressants and psychotherapy. Some patients with mild to moderate major depression may be helped by the provision of supportive care, problem-solving techniques, or specific psychotherapy, such as cognitive therapy alone. A patient's symptoms may seem to be a reaction to environmental factors alone, but that fact does not in itself preclude drug treatment.

Simplified diagnostic criteria for a major depressive episode

- Five or more of the following symptoms have been present nearly every day for 2 weeks; at least one of the symptoms is (a) or (b):
  - (a) Depressed mood most of the day
  - (b) Markedly diminished interest or pleasure in all or almost all activities most of the day
  - (c) Significant weight loss or weight gain or decrease or increase in appetite
  - (d) Insomnia or hypersomnia
  - (e) Psychomotor agitation or retardation
  - (f) Fatigue or loss of energy
  - (g) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional)
  - (h) Diminished ability to think or concentrate, or indecisiveness
  - (i) Recurrent thoughts of death, recurrent suicidal ideation, suicide attempt, or a specific plan for committing suicide.
- Symptoms cause clinically significant distress or impairment in important areas of functioning.
- Symptoms are not due to the direct psychological effects of a substance or a general medical condition.
- Symptoms are not better accounted for by bereavement.

Summary points

- In general, no antidepressant drug is clearly more effective than another.
- Outcome can be significantly improved by nonpharmacological factors, such as a good therapeutic alliance between the doctor and the patient.
- A practical approach is to prefer newer antidepressants in mildly and moderately depressed patients and tricyclic antidepressants in severely depressed patients.
- It usually takes 1 to 4 weeks of treatment with antidepressants before an effect is evident; this delay may be longer in elderly people.
- If patients do not respond to treatment, check compliance and reconsider the diagnosis before changing or adding drugs.
- After the initial treatment response, the drug should be continued at the same dose for at least 4 to 6 months.
- The dose should be gradually decreased over several weeks before withdrawal.

Therapeutic effect

About 60% of patients with major depression will respond to their initial drug treatment, regardless of the type of antidepressant used. Response is defined as a decrease of at least 50% in symptom ratings on a depression rating scale during the first 4 to 8 weeks of treatment.[3] Of the remaining 40% of patients, some respond partially, and some do not respond at all. It generally takes 1 to 4 weeks for an antidepressant to take effect.

In controlled trials, about 30% of patients respond to placebo. Thus, the overall clinical effect seems to be influenced by nonpharmacological factors. One important factor is the therapeutic alliance between the doctor and the patient.[4] The difference between drug and placebo effects increases as the severity of the depression increases. In milder forms of major depression, antidepressants may be no better than placebo, although patients with more chronic "low-grade" forms of depression, such as dysthymia, may benefit from antidepressants.[5,6]

The different types of antidepressant drugs are described in Table 1. Controversy exists about whether the newer antidepressants, particularly selective serotonin reuptake inhibitors, are as effective as tricyclic antidepressants. Several meta-analyses have recently compared the efficacy and tolerability of antidepressants. One meta-analysis found no differences in efficacy in inpatients or outpatients between selective serotonin reuptake inhibitors and tricyclic antidepressants.[7] Another suggested, however, that at least some tricyclic antidepressants may be more effective than selective serotonin reuptake inhibitors in inpatients, with the

strongest evidence for amitriptyline.[8] Moreover, well-conducted studies in severely depressed, hospitalized patients have indicated that clomipramine may be better than citalopram, paroxetine, and moclobemide.[9-11] Venlafaxine has been claimed to be more effective than selective serotonin reuptake inhibitors; this might be related, however, to the use of higher-than-standard doses.[12] Unambiguous evidence to support the claim of more rapid onset of action has not been obtained for any drug.

Adverse drug reactions

In general, differences in adverse reactions and toxicity are more important than the possible small differences in the clinical effects of various drugs. Tricyclic antidepressants cause peripheral anticholinergic effects such as dry mouth, constipation, and blurred vision, as well as central anticholinergic effects such as impaired concentration and confusion. Selective serotonin reuptake inhibitors predominantly cause nausea, diarrhea, anxiety, agitation, insomnia, and anorexia. In two recent meta-analyses, discontinuation rates due to adverse effects were generally higher in patients treated with tricyclic antidepressants than in patients treated with selective serotonin reuptake inhibitors.[7, 8] Long-term treatment with selective serotonin reuptake inhibitors can also cause sexual dysfunction, and patients affected by this may discontinue the drug.[13]

The adverse reactions associated with selective serotonin reuptake inhibitors also occur with other drugs that have a predominantly serotonergic profile, such as clomipramine, venlafaxine, and nefazodone, although nefazodone is less likely to cause insomnia and sexual dysfunction.[14] The limited data available suggest that only minor differences in adverse effects exist between the different selective serotonin reuptake inhibitors. The newer antidepressants are also occasionally implicated in more severe adverse reactions, such as seizures and hyponatremia. Some drugs have specific adverse effects, such as hypertension associated with venlafaxine and agranulocytosis with mianserin. An attempt to use clinical data to calculate the risk of a patient becoming manic as a result of treatment with antidepressants found that there was a rate of unipolar depression of less than 1% for placebo, tricyclic antidepressants, and selective serotonin reuptake inhibitors.[15]

The newer antidepressants are far less toxic than the older drugs. Of the tricyclic antidepressants, lofepramine has the lowest toxicity. There is no evidence that antidepressants are addictive.

Selecting a drug

When deciding which drug to prescribe, the context in which the drug is to be given is important. In general practice, most patients have mild to moderate depression and are probably less tolerant of adverse drug reactions.[16] In contrast, in severely depressed patients, a lack of effect is more important than the development of adverse effects. Thus a good approach is to prescribe newer, less toxic drugs for mildly and moderately depressed patients and to prescribe drugs acting on both serotonergic and noradrenergic neurotransmission, such as tricyclic antidepressants, in patients who are severely depressed. Among the newer drugs, there has been more experience with selective serotonin reuptake inhibitors.

Several specific conditions may, however, modify these general recommendations. The patient's response to drug treatment during previous depressive episodes is a valuable guide. Other important considerations are the adverse drug reactions experienced during previous treatment with antidepressants, concurrent somatic or other psychiatric diseases, and the use of other drugs that may interact with antidepressants.

Establishing the optimum dose

The delayed clinical response to antidepressants makes it difficult to establish the optimal dose quickly. The individual dose is usually decided by trial and error, with the patient's previous response being the most useful guide.

Tricyclic antidepressants have to be started at a low dose and increased gradually. Most selective serotonin reuptake inhibitors, however, can be administered at the recommended dose from the first day or after a few days of treatment at a lower dose. The doses of other, newer antidepressants can usually be increased more quickly than doses of tricyclic antidepressants. In primary care, patients commonly receive doses of tricyclic antidepressants that are lower than the recommended dose, whereas selective serotonin reuptake inhibitors are usually prescribed at the recommended dose.[17] This difference is probably caused by the different profiles of adverse reactions.

Table 1 *Classification of antidepressant drugs*

Type of antidepressant
Older antidepressants
*Tricyclic antidepressants**
Amitryptiline, amoxapine, clomipramine, desipramine, doxepin, imipramine, lofepramine, nortriptyline, protryptyline, trimipramine
*Other reuptake inhibitors**
Buproprion†, maprotiline, trazodone, viloxazine
Monoamine oxidase inhibitors (irreversible)
Isocarboxazid, phenelzine, tranlcypromine
Newer antidepressants
Selective serotonin reuptake inhibitors
Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Other reuptake inhibitors
Reboxetine‡, venlafaxine§
Monoamine oxidase inhibitors (reversible)
Moclobemide‖
Other antidepressants
Nefazodone¶, mianserin#, mirtazapine#

*Inhibits reuptake of serotonin or norepinephrine, or both. †Also inhibits reuptake of dopamine. ‡Inhibits reuptake of norepinephrine. §Inhibits reuptake of serotonin and norepinephrine. ‖Monoamine oxidase A inhibitor. ¶Inhibits reuptake of serotonin and blocks serotonin (5-HT2A) receptors. #Complex mechanism of action including presynaptic α_2 receptor blockade.

Reasons for consultation with or referral to a psychiatrist

- Uncertainty about diagnosis
- Severe depression, in particular with psychotic features or suicide risk
- Bipolar disorder
- Coexistence of other psychiatric disorders, such as alcoholism or severe personality disorder
- Failure to respond to treatment
- Intolerance of adverse effects

It is important to review patients' treatment regularly to check response, compliance, possible adverse drug reactions, and suicidal ideation. It has been suggested that the dose should be increased if patient compliance is good, yet there has been no response after 3 weeks. If there is a partial response, clinicians could wait another 2 weeks before increasing the dose.[18] For patients at risk of suicide, the amount of a drug prescribed in a single dose should be limited, particularly with the older, more toxic antidepressants.

The plasma concentrations of many antidepressants vary from 5- to 10-fold between patients given the same dose. This variability can mainly be explained by genetic differences in the metabolic capacity of hepatic cytochrome P-450 enzymes.[19] Therapeutic drug monitoring may therefore be helpful in establishing the optimum dose of these drugs and for investigating failures of treatment. The clinical value of routine monitoring has not been shown convincingly, however. Although concentration-effect relations have not been found for the newer antidepressants, drug monitoring might be justified in special cases, such as when low compliance or drug interactions are suspected.

Lack of response

When patients do not respond to the first-choice antidepressant at an adequate dose, compliance should be checked. If compliance is good, the diagnosis should be reconsidered and the patient should be investigated for the coexistence of another psychiatric disorder or a somatic or personality disorder. If further drug treatment is considered necessary, two strategies exist: the patient can be switched to a different antidepressant, or another antidepressant can be added to the existing regimen. There is little evidence to suggest which alternative is preferable. Many people believe that augmentation therapy should be handled by specialists.

If the decision is made to switch treatment, a drug with a different or broader mechanism of action should be chosen. Switching to a drug with an identical mechanism has been found to be effective in some cases, but the studies of this are not conclusive. It may be necessary for the patient to have a drug-free interval before starting the new treatment to avoid drug interactions. Irreversible and nonselective monoamine oxidase inhibitors should be used only in special cases, because of their potentially severe adverse effects.

The drugs most often added to antidepressant treatment are lithium, triiodothyronine, buspirone, pindolol, or, for patients receiving serotonin reuptake inhibitors, a compound acting on the noradrenergic system.[20] With the exception of lithium,[21] and to some extent triiodothyronine[22] and pindolol,[23] however, the evidence supporting augmentation is sparse. When antidepressant drugs are combined, the risk of drug interactions should always be taken into account. In certain situations, consultation with or referral to a psychiatrist should be considered (see box).

Length of treatment

Because the risk of relapse is higher during the first months after remission, treatment should generally be continued at the same dose for 4 to 6 months after the initial response to the drug.[24] The risk of relapse seems to be increased if there are residual symptoms[25] or if imminent or chronic life stresses exist. Longer treatment may therefore be warranted in such cases.

To avoid discontinuation reactions, treatment should be tapered down over several weeks before withdrawal. Although most of the focus has been on discontinuation reactions occurring during treatment with selective serotonin reuptake inhibitors, other antidepressants also cause such reactions.[26] Common discontinuation symptoms include dizziness, headache, paresthesias, nausea, anxiety, and irritability.[27]

Depression is recurrent in many patients. After the third, or in special cases the second, depressive episode, prophylactic treatment should be considered. For bipolar disorders, lithium or another mood-stabilizing drug is the treatment of choice, and referral to a psychiatrist is recommended. In unipolar depression, lithium and some antidepressants have been shown to reduce the risk of recurrence.[28] The length of prophylaxis has to be decided on a case-by-case basis. Some patients will benefit from treatment for long periods, or even for life. Although the doses required for prophylaxis are unclear, it is generally recommended that the dose to which the patient initially responded should be used.

Drug interactions

Several clinically important pharmacokinetic and pharmacodynamic drug interactions have been reported for antidepressants. The risk of drug interactions should therefore always be considered before treatment with an antidepressant is planned in combination with another drug. Antidepressants are metabolized by the hepatic cytochrome P-450 system.[19] Fluoxetine, fluvoxamine, and paroxetine, in particular, are potent inhibitors of cytochrome P-450 isoenzymes and may cause important pharmacokinetic drug interactions.[29] Serotonin reuptake inhibitors should not be combined with monoamine oxidase inhibitors because of the risk of the serotonin syndrome.[30] In

addition, a drug-free interval is usually needed when treatment switches between these two drug groups.

Pregnancy and lactation

Tricyclic antidepressants have been widely used during the first trimester of pregnancy and have not been shown to have any teratogenic effects. Moreover, several studies have concluded that fluoxetine does not increase the rate of malformations when used in the first trimester.[31, 32] Little or no information is available on the possible teratogenic effects of other, newer antidepressants with the exception of fluvoxamine, paroxetine, and sertraline.[33]

Neonatal adaptation disturbances have been reported after exposure to tricyclic antidepressants in the third trimester, and a recent study indicates that fluoxetine may also cause such symptoms.[31] Based on current knowledge, it is reasonable to assume that all antidepressants carry this risk. A study of preschool children suggested that exposure to antidepressants in utero does not adversely affect long-term neurodevelopment.[34]

With the exception of doxepin, maternal treatment with tricyclic antidepressants does not seem to harm breast-fed infants.[35] Although some concern has been expressed about use of fluoxetine while breastfeeding, no detrimental effects have been reported for other selective serotonin reuptake inhibitors, and the exposure of the infant to these drugs is lower than for fluoxetine. Little information is available, however, for most newer antidepressants.[35]

Treatment of elderly people

Elderly people are generally more susceptible to anticholinergic effects, so treatment with the newer antidepressants is preferred. If a tricyclic antidepressant must be used, drugs with pronounced anticholinergic effects, such as amitriptyline, should be avoided, and the dose should be lower than that given to younger patients. The antidepressant effect may be more delayed in elderly people than in younger patients, and treatment may need to be continued for longer than 6 months. Elderly people often take drugs for somatic disorders, and the risk of specific drug interactions should be taken into account.

Costs

Questions are being raised about whether the newer antidepressants are worth their considerably higher prices when compared with the tricyclic antidepressants. Studies have found an advantage for the newer antidepressants.[36] Most of these studies, however, used models and simulations based on estimations from clinical trials or meta-analyses rather than data from population studies. To answer these questions conclusively, health economic evaluations need to be carried out in long-term, naturalistic, prospective, and randomized studies of antidepressants in primary care.

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